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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	11

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/644,498	SALIN-NORDSTROM, TUIJA HELINA	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,15,16,23-35,38-43,45-59 and 64* is/are pending in the application.

4a) Of the above claim(s) *15,16,23,25-31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-12,24,32,33,38-43,46-59 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 27 December 2002 (Paper No. 10) has been entered in full. Claims 1, 4, 6, 12, 24, 39, 46, 48, 49, and 57 have been amended and claim 64 has been added. Claims 2-3, 13-14, 17-22, 36-37, and 44-45 have been cancelled. Claims 15-16, 23, 25-31, 34-35 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 1, 4-12, 24, 32-33, 38-43, 46-59, and 64 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The objection to the specification as set forth at pp. 3 ¶ 4-6 of the previous Office Action (Paper No. 9, 20 September 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 27 December 2002).

4. The objection to the claims as set forth at pp. 3 ¶ 7 of the previous Office Action (Paper No. 9, 20 September 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 10, 27 December 2002).

Maintained Objections And/Or Rejections

5. Claims 1-14, 17-22, 24, 32-33, and 36-59 and 64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth in at pp. 3-8 ¶ 8-17 of the previous Office Action (Paper No. 9, 20 September 2002). Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

6. The Applicant traverses the 35 USC 112 1st paragraph rejection of claims 1-14, 17-22, 24, 32-33, and 36-59 as set forth in at pp. 3-8 ¶ 8-17 of the previous Office Action (Paper No. 9, 20 September 2002) on the grounds that the invention is novel, unobvious, described by the Applicant, has utility, and a person of ordinary skill in the art is able to practice the invention without isolating stem cells, (pp. 9 **II**, Paper No. 10). It is noted that the Applicant has cancelled claims 2-3, 13-14, 17-22, 36-37, and 44-45 therefore the rejection is maintained on claims 1, 4-12, 24, 32-33, 38-43, 46-59 (as amended in Paper No. 10) and extended to cover claim 64 (added in Paper No. 10).

7. The Applicant discloses that no stem cells are necessary for the practicing of the claimed invention (pp. 10 **III**). The Examiner *accepts* this argument as the claims are directed to "astrocytes" and "glia" neither of which are stem cells [Gage et al. (1995) "Isolation, Characterization, and Use of Stem Cells from the CNS." Annu. Rev. Neurosci. 18: 159-192].

8. The Applicant traverses the rejection under 35 USC 112 1st paragraph on the grounds that claims 4-9, 38, 57, 59, and 64 are directed to a single species of growth factor (bFGF) and a specific species of cell (astrocytes) thus it would represent no undo burden of experimentation to practice the claimed invention. The Examiner has *withdrawn* the objection to the claims for reciting nonelected species. The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 1, 4-12, 24, 32-33, 38-43, 46-59 and 64.

9. Concerning the "Wands factors", the Applicant discloses that the breadth of the claims does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**A**) pp. 12]. The Examiner has taken this into consideration and the argument is not found persuasive.

In regards to Appendix A [Morshead et al. (2002) "Selective Ablation of GAP Positive Cells in the Adult Subependmya Results in the Loss of Neurosphere Formation." SFN Abstract] and Appendix B [Imura et al. (2002) "The Predominant Neural Stem Cell Isolated from Postnatal Peri-Ventricular Germinal Zone is a GFAP-Expressing Glia." SFN Abstract]. Both references are concerned with "neural stem cells (NSC)" while the claims are directed to "glia" and "astrocytes". It is well known the art that multipotent $GFAP^+$ cells reside in the subventricular zone [Rao (1999) "Multipotent and Restricted Precursors in the Central Nervous System" The Anatomical Record 257: 137-148] however; these cells are considered stem cells and therefore do not meet the limitations of "astrocytes".

10. Concerning the "Wands factors", the Applicant discloses that the nature of the invention does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**B**) pp. 13]. The Examiner has taken this into consideration and the argument is not found persuasive.

The Examiner maintains that the invention is not supported by the specification or the prior art concerning the action of bFGF or members of the FGF family on astrocytes. Bikfalvi et al. (1997) ["Biological Roles of Fibroblast Growth Factor-2." Endocrine Reviews 18(1): 26-45 (**IDS**)] teaches that FGF-2 varies in its effects on glia, astrocytes and oligodendrocytes. While FGF-2 can induce dedifferentiation and proliferation of oligodendrocytes, these glia remain

committed to the oligodendrocytic linage (pp. 34). Bikfalvi et al. (1997) teaches that FGF-2 will induce proliferation of astrocytes (pp. 34). A person of ordinary skill in the art would not have evidence or art to guide them through the invention.

11. Concerning the "Wands factors", the Applicant discloses that the state of the prior art does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**C**) pp. 13]. The Examiner has taken this into consideration and the argument *is* persuasive.

In regards to the art, it teaches the contrary to the claimed invention. Lee et al. [(2000) "Gliogenesis in the Central Nervous System." GLIA 30: 105-121], this references discusses glial restricted precursors (GRP). It is important to distinguish between the multipotent $GFAP^+$ cells referred to in Lee et al. (2000) as GRP and "astrocytes" (Figure 3; Table 1; Figure 5). Lee et al. (2000) discloses that treatment of GRP with FGF (including but not limited to bFGF) causes only proliferation and not differentiation (pp. 112; pp. 115; Table 2). In addition, GRP are incapable of producing neurons (pp. 108). It is of note that Lee et al. (2000) discloses that human fetal cultures can co-express GFAP and neuronal markers (pp. 107). Therefore it is unclear whether bFGF, regardless of the time of exposure, could coerce glia, even glial progenitor cells, to produce neurons.

12. Concerning the "Wands factors", the Applicant discloses that the skill level of one of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**D**) pp. 13]. The Examiner has taken this into consideration and the argument is not persuasive.

The level of one of ordinary skill in the art is not a point of discussion in terms of whether the applicant is capable or not. The Examiner rejects the invention on the grounds that

the art teaches to the contrary of the claimed invention and the specification fails to provide adequate evidence to convince or otherwise guide a person of ordinary skill in the art to make or use the invention.

13. Concerning the "Wands factors", the Applicant discloses that the level of predictability in the art does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**E**) pp. 13]. The Examiner has taken this into consideration and the argument is not persuasive.

In regards to the level of predictability in the art, while FGF-2 is a well-known growth factor, the effects claimed by the Applicant are contrary to the prior art and not supported by the specification. In respect to Appendix A [Morshead et al. (2002) "Selective Ablation of GAP Positive Cells in the Adult Subependmya Results in the Loss of Neurosphere Formation." SFN Abstract] and Appendix B [Imura et al. (2002) "The Predominant Neural Stem Cell Isolated from Postnatal Peri-Ventricular Germinal Zone is a GFAP-Expressing Glia." SFN Abstract]. Both references are concerned with "neural stem cells (nsc)" while the claims are directed to "glia" and "astrocytes". It is well known the art that multipotent $GFAP^+$ cells reside in the subventricular zone [Rao (1999) "Multipotent and Restricted Precursors in the Central Nervous System" The Anatomical Record 257: 137-148] however; these cells are considered stem cells and therefore do not meet the limitations of "astrocytes".

Furthermore, Rao et al. [(1998) "A Tripotential Glial Precursor Cell is Present in the Developing Spinal Cord." PNAS 95: 3996-4001], this reference discusses a "tripotential glial precursor cell population from spinal cords of E13.5 rats". Again, these cells are embryonic stem cells and thus do not meet the limitations of "astrocytes".

14. Concerning the "Wands factors", the Applicant discloses that amount of direction provided by the inventor enables a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**F**) pp. 14]. The Examiner has taken this into consideration and the argument is not persuasive.

The Examiner maintains that the specification asserts that neural stem cells can be isolated; cultured to form astrocytes, and that these astrocytes can be caused to turn into a number of other neural cells by treatment with bFGF. Example 6.1.1 speaks to isolation of human neural stem cells, but does not give any experimental detail as to how these stem cells were isolated. One skilled in this art would be unable to repeat the experiment in the absence of these details. In Example, 6.1.2, more experimental details are provided as to how to isolate neural stem cells from an animal, but the example is silent with respect to the animal from which the cells are isolated. Furthermore, the specification is silent on how non-stem, non-embryonic, non-multipotent precursor, astrocytes can form multiple cell times. No direction of how adult astrocytes can be induced to become neurons is given.

15. Concerning the "Wands factors", the Applicant discloses that the working examples in the specification enable a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**G**) pp. 14]. The Examiner has taken this into consideration and the argument is not persuasive.

The Examiner maintains that the specification asserts that neural stem cells can be isolated; cultured to form astrocytes, and that these astrocytes can be caused to turn into a number of other neural cells by treatment with bFGF. Example 6.1.1 speaks to isolation of human neural stem cells, but does not give any experimental detail as to how these stem cells

were isolated. One skilled in this art would be unable to repeat the experiment in the absence of these details. In Example, 6.1.2, more experimental details are provided as to how to isolate neural stem cells from an animal, but the example is silent with respect to the animal from which the cells are isolated. Furthermore, the specification is silent on how non-stem, non-embryonic, non-multipotent precursor, astrocytes can form multiple cell times. No examples of adult astrocytes become neurons upon treatment with bFGF are given.

16. Concerning the "Wands factors", the Applicant discloses that the quantity of experimentation needed to make and use the invention does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**H**) pp. 14-15]. The Examiner has taken this into consideration and the argument is not persuasive.

Since no working examples are given in the specification and the prior art teaches the contrary to the claimed invention, the Examiner maintains that it would represent an onerous burden of experimentation to make and use the invention. Concerning, astrocyte subtypes, see Rao (2000) Table 1.

Therefore the rejection of claims 1, 4-12, 24, 32-33, 38-43, 46-59, and 64 under 35 USC 112 1st paragraph is *maintained.*

17. Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as set forth in at pp. 3-8 ¶ 8-17 of the previous Office Action (Paper No. 9, 20 September 2002).

18. The Applicant traverses the rejection under 35 USC 112 1st paragraph on the grounds that claims 46-48 are specifically directed to a specific species of growth factor, bFGF, and specific class of cell (glial) so that a person of ordinary skill would not need to perform significant amounts of experimentation to perform the claimed invention (Paper No. 10 **V** pp. 15). The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 46-48.

19. Concerning the "Wands factors", the Applicant discloses that the breadth of the claims is not a factor because the number of neuronal subtypes is not relevant [(**A**) pp. 16]. The Examiner has taken this into consideration and the argument is not found persuasive.

The Examiner maintains that the invention is not supported by the specification or the prior art concerning which if any neuron cells are produced from glia following bFGF treatment. As noted above, Bikfalvi et al. (1997) ["Biological Roles of Fibroblast Growth Factor-2." Endocrine Reviews 18(1): 26-45 (**IDS**)] teaches that FGF-2 varies in its effects on glia, astrocytes and oligodendrocytes. While FGF-2 can induced dedifferentiation and proliferation of oligodendrocytes, these glia remain committed to the oligodendrocytic linage (pp. 34). Furthermore Bikfalvi et al. (1997) teaches that FGF-2 will induce proliferation of astrocytes (pp. 34). A person of ordinary skill in the art would not have a reasonable expectation of success in treating glia with bFGF to produce neurons of any kind.

20. Concerning the "Wands factors", the Applicant discloses that the nature of the invention is not so complex as to impede a person of ordinary skill from practicing it [(**B**) pp. 17]. The Examiner has taken this into consideration and the argument is not found persuasive.

The Examiner maintains that the invention is not supported by the specification or the prior art concerning the action of bFGF or members of the FGF family on astrocytes. As noted

above, Bikfalvi et al. (1997) ["Biological Roles of Fibroblast Growth Factor-2." Endocrine Reviews 18(1): 26-45 (**IDS**)] teaches that FGF-2 varies in its effects on glia, astrocytes and oligodendrocytes. While FGF-2 can induced dedifferentiation and proliferation of oligodendrocytes, these glia remain committed to the oligodendrocytic linage (pp. 34). Bikfalvi et al. (1997) teaches that FGF-2 will induce proliferation of astrocytes (pp. 34). A person of ordinary skill in the art would not have evidence or art to guide them through the invention.

21. Concerning the "Wands factors", the Applicant discloses that the state of the prior art does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**C**) pp. 17]. The Examiner has taken this into consideration and the argument *is* persuasive.

In regards to the art, it teaches the contrary to the claimed invention. Lee et al. [(2000) "Gliogenesis in the Central Nervous System." GLIA 30: 105-121], this references discusses glial restricted precursors (GRP). It is important to distinguish between the multipotent $GFAP^+$ cells referred to in Lee et al. (2000) as GRP and "astrocytes" (Figure 3; Table 1; Figure 5). Lee et al. (2000) discloses that treatment of GRP with FGF (including but not limited to bFGF) causes only proliferation and not differentiation (pp. 112; pp. 115; Table 2). In addition, GRP are incapable of producing neurons (pp. 108). It is of note that Lee et al. (2000) discloses that human fetal cultures can co-express GFAP and neuronal markers (pp. 107). Therefore it is unclear whether bFGF, regardless of the time of exposure, could coerce glia, even glial progenitor cells, to produce neurons.

22. Concerning the "Wands factors", the Applicant discloses that the skill level of one of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**D**) pp. 17]. The Examiner has taken this into consideration and the argument is not persuasive.

The level of one of ordinary skill in the art is not a point of discussion in terms of whether the applicant is capable or not. The Examiner rejects the invention on the grounds that the art teaches to the contrary of the claimed invention and the specification fails to provide adequate evidence to convince or otherwise guide a person of ordinary skill in the art to make or use the invention.

23. Concerning the "Wands factors", the Applicant discloses that the level of predictability in the art does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**E**) pp. 17]. The Examiner has taken this into consideration and the argument is not persuasive.

In regards to the level of predictability in the art, while FGF-2 is a well-known growth factor, the effects claimed by the Applicant are contrary to the prior art and not supported by the specification. It is well known the art that multipotent $GFAP^+$ cells reside in the subventricular zone [Rao (1999) "Multipotent and Restricted Precursors in the Central Nervous System" The Anatomical Record 257: 137-148] however; these cells are considered stem cells and therefore do not meet the limitations of "astrocytes". Furthermore, concerning Alberts et al. (page 1064, Appendix C) as noted above, a common embryonic origin is not a guarantee of "transdifferentiation".

In regards to Imura et al. ["The Predominant Neural Stem Cell Isolated from Postnatal Peri-Ventricular Germinal Zone is a GFAP-Expressing Glia." SFN Abstract (2002)], actually

teaches art contrary to the invention. The present invention is drawn to "glia" not neural stem cells (NSC), whether GFAP positive or not, as discussed in Imura et al. (2002): "We concluded that a GFAP-expressing radial glia, but not stellate astrocytes are NSCs." Imura further notes that some not all $GFAP^+$ cells are NSCs, therefore as a NSC, the yielding of three cells types is due to differentiation not transdifferentiation. Taken together, these results show that the multipotent $GFAP^+$ cells are NSCs and not all $GFAP^+$ cells are NSCs thus establishing a degree of unpredictability in practicing the present invention.

24. Concerning the "Wands factors", the Applicant discloses that amount of direction provided by the inventor enables a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**F**) pp. 18]. The Examiner has taken this into consideration and the argument is not persuasive.

The Examiner maintains that the specification asserts that neural stem cells can be isolated; cultured to form astrocytes, and that these astrocytes can be caused to turn into a number of other neural cells by treatment with bFGF. Example 5.7 speaks to a generic screening method to identify neuronal and glial cells immunopositive to β-tubulin III and MAP2ab for neurons and GFAP for astrocytes. The positive control included in the method is bFGF, but as discussed above, the prior art teaches the bFGF does not have the claimed effect. Furthermore a person of ordinary skill in the art at the time of the invention would not have a reasonable expectation of success due to the lack of a positive control.

25. Concerning the "Wands factors", the Applicant discloses that the working examples in the specification enable a person of ordinary skill in the art at the time of the invention from

practicing the claimed invention [(**G**) pp. 18-19]. The Examiner has taken this into consideration and the argument is not persuasive.

The Examiner maintains that the specification asserts that neural stem cells can be isolated; cultured to form astrocytes, and that these astrocytes can be caused to turn into a number of other neural cells by treatment with bFGF. Examples 6.0, 6.1, 6.1.1, 6.1.2, and 6.1.3 speaks to the culturing of astrocytes derived from human neural stem cells. In light of Imura et al. and Rao et al. it is clear that many NSCs or astrocyte progenitor cells (APCs) can be $GFAP^+$ thus casting a shadow on the claim that the cells used in the Examples are indeed astrocytes and not NSCs or APCs or GPCs. One skilled in this art would be unable to repeat the experiment in the absence of these details. In Example, 6.1.2, more experimental details are provided as to how to isolate neural stem cells from an animal, but the example is silent with respect to the animal from which the cells are isolated. Furthermore, the specification is silent on how non-stem, non-embryonic, non-multipotent precursor, astrocytes can form multiple cell times. No examples of adult astrocytes become neurons upon treatment with bFGF are given.

Figures 1 and 2 do not show cells that are immunopositive for a neuronal or oligodendrocyte markers, a standard set by the Applicant for evaluation the effectiveness of the treatment. Figure 3 shows three separate panels each with cells immunopositive for a marker either β-tubulin III, MAP2ab, and CNPase. While each individual marker is accepted by the Examiner to be indicative of neurons for β-tubulin III and MAP2ab, and oligodendrocytes for CNPase, the figure legend only states "cells" (pp. 8) and the Examples are all drawn to neuronal stem cells, not astrocytes. Therefore, the figures do not depict the results of bFGF treatment of astrocytes as claimed in the present application.

26. Concerning the "Wands factors", the Applicant discloses that the quantity of experimentation needed to make and use the invention does not impede a person of ordinary skill in the art at the time of the invention from practicing the claimed invention [(**H**) pp. 19-20]. The Examiner has taken this into consideration and the argument is found persuasive.

The Examiner accepts that a finite number (9) of glial subtypes are known. Thus, the sheer number of glial cell types does not present an onerous burden of experimentation.

Therefore the rejection of claims 46-48 under 35 USC 112 1st paragraph is *maintained.*

27. Claims 1, 10-12, 32, 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as set forth in at pp. 3-8 ¶ 8-17 of the previous Office Action (Paper No. 9, 20 September 2002).

28. The Applicant traverses the rejection under 35 USC 112 ¶1 on the grounds that claims 1, 10-12, 32, 40-43 are directed to the FGF family and to a specific species of cell (astrocytes) thus it would represent no undo burden of experimentation to practice the claimed invention (Paper No. 10 **VI** pp. 20). The Examiner has *withdrawn* the objection to the claims for reciting nonelected species. The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 1, 4-12, 24, 32-33, 38-43, 46-59 and 64.

Concerning radial glia Chanas-Sacre et al. ["Radial Glia Phenotype: Origin, Regulation, and Transdifferentiation" (2000) Journal of Neuroscience Research 61: 357-363] teaches that radial glia (a specific species of cell) can transdifferentiate into astrocytes, a GFAP+ mature form of glia. In addition, prior to the transdifferentiation into astrocytes, the radial glia are capable of

forming various cell types, including neurons (Abstract). However, Chanas-Sacre et al. (2000) goes on to describe the radial glia as neural stem cells (pp. 358 2nd column). Chanas-Sacre et al. (2000) teaches that astrocytes with stem cell characteristics (therefore NSCs) loose the ability to differentiate after postnatal day 11 (pp. 350 1st column). Radial glia, however, can retain the ability to differentiate and to regain properties of radial glia (pp. 360 2nd column; Figure 1). Also, no cell-derived factors were known by Chanas-Sacre et al. (2000) to influence the radial glia in vitro (pp. 361 2nd column). Thus, the art teaches the contrary to the claimed invention. Radial glia, a form of neural stem cells (NSC), have the ability to transdifferentiate, dedifferentiate, and differentiate but not $GFAP^+$ astrocytes *per se*.

29. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as set forth in at pp. 3-8 ¶ 8-17 of the previous Office Action (Paper No. 9, 20 September 2002).

30. The Applicant traverses the rejection under 35 USC 112 ¶1 on the grounds that claim 39 is directed to the FGF family and to a specific species of cells (glia) thus it would represent no undo burden of experimentation to practice the claimed invention (Paper No. 10 **VII** pp. 21). The Applicant's argument is found persuasive concerning undo experimentation due to a large number of glial cell types. The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 1, 4-12, 24, 32-33, 38-43, 46-59 and 64.

31. The Applicant traverses the rejection under 35 USC 112 ¶1 on the grounds that claims 49-56 are directed to a single species of growth factor (bFGF) and a specific species of cell (astrocytes) thus it would represent no undo burden of experimentation to practice the claimed

invention (Paper No. 10 **VIII** pp. 21). The Examiner has *withdrawn* the objection to the claims for reciting nonelected species. The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 1, 4-12, 24, 32-33, 38-43, 46-59 and 64.

Since the Applicant has failed to persuade the Examiner that treatment with growth factors, based on the specification and the prior art, will cause a glia cell, an astrocyte or otherwise to become a neuron, an oligodendrocyte, or astrocyte, the rejection 35 USC 112 ¶1 is *maintained.* It is noted that the current claims of 49-59 are drawn to a screening method. However, as discussed above, since no evidence exists that glia become neurons after treatment with growth factors, a person of ordinary skill in the art would not have any reasonable expectation of success in practicing the claimed invention. Furthermore, it presents an undo burden of experimentation to first demonstrate that FGF-2, the control, will force astrocytes to become neurons before attempting a screening assay to identify other agents with similar activity. Therefore the rejection under 35 USC 112 ¶1 is *maintained* for claims 49-59.

32. Finally, the Applicant's argument has been taken into full consideration and is not found persuasive. The Applicant has failed to show any convincing evidence in the prior art or specification of "transdifferentiation", specifically the treatment of astrocytes with bFGF to become "multipotent" cells and thereafter, neurons, astrocytes, and oligodendrocytes. It is well established in the art that mammals continue to harbor stem cells [also known as "multipotent" or "progenitor" cells see Gage et al. (1995) "Isolation, Characterization, and Use of Stem Cells from the CNS." Annu. Rev. Neurosci. 18: 159-192] in the central nervous system into adulthood. However, the present application, particularly the claims, is concerned with astrocytes, and hence, not stem cells. Therefore the Applicant's discussion of the differentiation potential of

stem cells or multipotent cells, while accurate, is not relevant. The Applicant must show convincing evidence in the form of the specification, drawings, and/or art references of enabling examples of mature astrocytes becoming neurons, astrocytes, and oligodendrocytes following the claimed treatment with bFGF. Therefore, the rejection of claims 1, 4-12, 24, 32-33, 38-43, 46-59, and 64 under 35 USC 112 ¶1 is maintained.

33. Claim 12 recites the limitation "claim 3" in the first line. There is insufficient antecedent basis for this limitation in the claim. Claim 3 has been canceled and therefore cannot be the parent claim of a dependent claim.

Summary

34. No claims are allowed.

35. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher J. Nichols whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elyabeth C. Kemmerer

CJN
February 21st, 2003